STN- Structure Search 12/28/07

10/516,839

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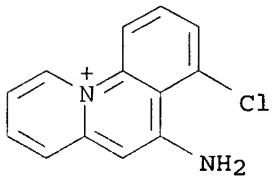
L4 ANSWER 1 OF 20 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2007:905676 CAPLUS
DOCUMENT NUMBER: 147:419267
TITLE: Anticancer medicines in development: assessment of bioactivity profiles within the National Cancer Institute anticancer screening data
AUTHOR(S): Covell, David G.; Huang, Ruili; Wallqvist, Anders
CORPORATE SOURCE: Developmental Therapeutics Program, Screening Technologies Branch, Laboratory of Computational Technologies and Laboratory of Computational Technologies, Science Applications International Corporation-Frederick, Inc., National Cancer Institute-Frederick, Frederick, MD, USA
SOURCE: Molecular Cancer Therapeutics (2007), 6(8), 2261-2270
CODEN: MCTOCF; ISSN: 1535-7163
PUBLISHER: American Association for Cancer Research
DOCUMENT TYPE: Journal
LANGUAGE: English

AB We present an anal. of current anticancer compds. that are in phase I, II, or III clin. trials and their structural analogs that have been screened in the National Cancer Institute (NCI) anticancer screening program. Bioactivity profiles, measured across the NCI 60 cell lines, were examined for a correspondence between the type of cancer proposed for clin. testing and selective sensitivity to appropriately matched tumor subpanels in the NCI screen. These results find strongest support for using the NCI anticancer screen to select analog compds. with selective sensitivity to the leukemia, colon, central nervous system, melanoma, and ovarian panels, but not for renal, prostate, and breast panels. These results are extended to applications of two-dimensional structural features to further refine compound selections based on tumor panel sensitivity obtained from tumor screening results.

IT 191091-50-6, NSC 679795
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(anticancer medicines in development and assessment of bioactivity profiles within the National Cancer Institute anticancer screening data)
RN 191091-50-6 CAPLUS
CN Benzo[c]quinolizinium, 6-amino-7-chloro-, chloride (1:1) (CA INDEX NAME)

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REFERENCE COUNT: 39 THERE ARE 39 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 2 OF 20 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2007:512914 CAPLUS
DOCUMENT NUMBER: 146:475125
TITLE: MPB-07 reduces the inflammatory response to

Pseudomonas aeruginosa in cystic fibrosis bronchial cells

AUTHOR(S): Dechecchi, Maria Cristina; Nicolis, Elena; Bezzerri, Valentino; Vella, Antonio; Colombatti, Marco; Assael, Baroukh Maurice; Mettey, Yvette; Borgatti, Monica; Mancini, Irene; Gambari, Roberto; Becq, Frederic; Cabrini, Giulio

CORPORATE SOURCE: Laboratory of Molecular Pathology, Cystic Fibrosis Center, University Hospital of Verona, University of Verona, Verona, Italy

SOURCE: American Journal of Respiratory Cell and Molecular Biology (2007), 36(5), 615-624
CODEN: AJRBEL; ISSN: 1044-1549

PUBLISHER: American Thoracic Society

DOCUMENT TYPE: Journal

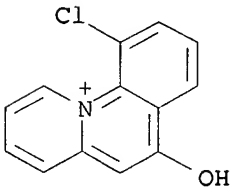
LANGUAGE: English

AB Chronic lung inflammation in cystic fibrosis (CF) is specifically characterized by predominant endobronchial neutrophil infiltrates, colonization by P. aeruginosa, and elevated levels of cytokines and chemokines, first of all IL-8. The extensive inflammatory process in CF lungs is the basis of progressive tissue damage and is largely considered detrimental, making anti-inflammatory approaches a relevant therapeutic target. This neutrophil-dominated inflammation seems to be related to an excessive proinflammatory signaling, originating from the same surface epithelial cells expressing the defective CF transmembrane conductance regulator (CFTR) protein, although the underlying mechanisms have not been completely elucidated. To investigate the relation between defective CFTR and the inflammatory response to P. aeruginosa in CF airway cells, the authors studied the effect of the ΔF508 CFTR corrector, benzo[c]quinolizinium (MPB)-07. CF bronchial epithelial IB3-1 and CuFi-1 cells overproduced the inflammatory mols., IL-8 and intercellular adhesion mol. (ICAM)-1, in response to P. aeruginosa, compared with the wild-type, CFTR-expressing bronchial cells, S9, and NuLi-1 cells. In both IB3-1 and CuFi-1 cells, the corrector MPB-07 dramatically reduces the IL-8 and ICAM-1 mRNA expression elicited by P. aeruginosa infection. Correction of CFTR-dependent Cl- efflux was confirmed in MPB-07-treated IB3-1 and CuFi-1 cells. Thus, the ΔF508 CFTR corrector MPB-07 produces an anti-inflammatory effect in CF bronchial cells exposed to P. aeruginosa in vitro.

IT 191091-55-1, MPB-07
RL: DMA (Drug mechanism of action); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(MPB-07 reduces inflammatory response to Pseudomonas aeruginosa in cystic fibrosis bronchial cells)

RN 191091-55-1 CAPLUS

CN Benzo[c]quinolizinium, 10-chloro-6-hydroxy-, chloride (1:1) (CA INDEX NAME)

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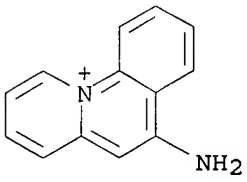
REFERENCE COUNT: 50 THERE ARE 50 CITED REFERENCES AVAILABLE FOR THIS

RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 3 OF 20 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2005:409850 CAPLUS
Correction of: 2005:155222
DOCUMENT NUMBER: 143:248214
Correction of: 142:240244
TITLE: Product class 7: quinolizinium salts and benzo analogues
AUTHOR(S): Ihmels, H.
CORPORATE SOURCE: Germany
SOURCE: Science of Synthesis (2005), 15, 907-945
CODEN: SSCYJ9
PUBLISHER: Georg Thieme Verlag
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
AB A review primarily covering methods of preparation of the quinolizinium, benzo[b]quinolizinium, benzo[c]quinolizinium, and benzo[a]quinolizinium salts. Synthetic methods include cyclization, aromatization, and substituent modification.
IT 71711-63-2P
RL: SPN (Synthetic preparation); PREP (Preparation)
(preparation of quinolizinium salt derivs. via cyclization, aromatization and substituent modification)
RN 71711-63-2 CAPLUS
CN Benzo[c]quinolizinium, 6-amino-, chloride (9CI) (CA INDEX NAME)




● Cl⁻

L4 ANSWER 4 OF 20 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2005:408095 CAPLUS
DOCUMENT NUMBER: 142:457132
TITLE: Use of deoxynojirimycin compound glucosidase inhibitors for the treatment of cystic fibrosis
INVENTOR(S): Becq, Frederic; Norez, Caroline
PATENT ASSIGNEE(S): Centre National de la Recherche Scientifique CNRS, Fr.; Universite de Poitiers
SOURCE: Fr. Demande, 31 pp.
CODEN: FRXXBL
DOCUMENT TYPE: Patent
LANGUAGE: French
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

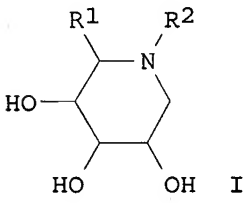
| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| FR 2861991 | A1 | 20050513 | FR 2003-13134 | 20031107 |
| AU 2004289083 | A1 | 20050526 | AU 2004-289083 | 20041105 |
| CA 2545133 | A1 | 20050526 | CA 2004-2545133 | 20041105 |
| WO 2005046672 | A2 | 20050526 | WO 2004-FR2858 | 20041105 |

WO 2005046672 A3 20050915
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW
RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

| | | | | | |
|---|---|---|---|---|---|
| EP 1680105 | A2 | 20060719 | EP 2004-805405 | | 20041105 |
| BR 2004016228 | A | 20070102 | BR 2004-16228 | | 20041105 |
| CN 1897933 | A | 20070117 | CN 2004-80038221 | | 20041105 |
| JP 2007510699 | T | 20070426 | JP 2006-538890 | | 20041105 |
| MX 2006PA05086 | A | 20061211 | MX 2006-PA5086 | | 20060504 |
| IN 2006DN02546 | A | 20070824 | IN 2006-DN2546 | | 20060505 |
| NO 2006002617 | A | 20060725 | NO 2006-2617 | | 20060607 |
| US 2007213357 | A1 | 20070913 | US 2007-578328 | | 20070122 |
| PRIORITY APPLN. INFO.: | | | FR 2003-13134 | A | 20031107 |
| | | | WO 2004-FR2858 | W | 20041105 |

OTHER SOURCE(S): MARPAT 142:457132


GI



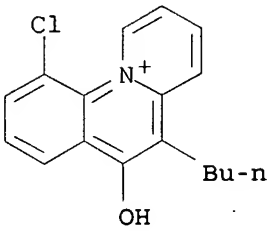

I


AB The invention discloses the use of selected inhibitors of glucosidase, particularly compds. I [R1 = Me, CH2OH; R2 = H, C1-5 alkyl, or R1C(a)NR2 form Q], for the preparation of a medicament for the treatment of cystic fibrosis.


IT 396712-16-6, MPB 91
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(deoxynojirimycin compound glucosidase inhibitors for treatment of cystic fibrosis)

RN 396712-16-6 CAPLUS

CN Benzo[c]quinolizinium, 5-butyl-10-chloro-6-hydroxy-, chloride (9CI) (CA INDEX NAME)

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REFERENCE COUNT: 7 THERE ARE 7 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 5 OF 20 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2004:420778 CAPLUS
DOCUMENT NUMBER: 141:21805
TITLE: The cystic fibrosis mutation G1349D within the signature motif LSHGH of NBD2 abolishes the activation of CFTR chloride channels by genistein
AUTHOR(S): Melin, Patricia; Thoreau, Vincent; Norez, Caroline; Bilan, Frederic; Kitzis, Alain; Becq, Frederic
CORPORATE SOURCE: Institut de Physiologie et Biologie Cellulaires, Universite de Poitiers, CNRS UMR 6187, Poitiers, 86022, Fr.
SOURCE: Biochemical Pharmacology (2004), 67(12), 2187-2196
CODEN: BCPCA6; ISSN: 0006-2952
PUBLISHER: Elsevier Science B.V.
DOCUMENT TYPE: Journal
LANGUAGE: English

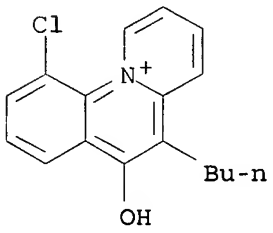
AB Cystic fibrosis (CF) is a common lethal genetic disease caused by autosomal recessive mutations of the cystic fibrosis transmembrane conductance regulator (CFTR) chloride channel that belongs to the ATP-Binding Cassette (ABC) family of transporters. The class III CF mutations G551D and G1349D are located within the "signature" sequence LSGGQ and LSHGH of NBD1 and NBD2, resp. The authors have constructed by site-directed mutagenesis vectors encoding green fluorescent protein (GFP)-tagged wild-type (wt) CFTR or CFTR containing delF508, G551D, G1349D and G551D/G1349D to study their pharmacol. after transient expression in COS-7 cells. The authors show that IBMX and the benzo[c]quinolizinium derivative MPB-91 stimulates the activity of G1349D-, G551D- and G551D/G1349D-CFTR only in the presence of cAMP-promoting agents like forskolin or cpt-cAMP. Similar half-maximal effective concns. (EC50) of MPB-91 (22-36 μM) have been determined for wt-, G551D-, G1349D- and G551D/G1349D-CFTR. The isoflavone genistein stimulates wild-type (wt)- and delF508-CFTR channel activity in a non-Michaelis-Menten manner. By contrast, the response of G1349D- and G551D-CFTR to genistein is dramatically altered. First, genistein is not able to stimulate G1349D- and G551D/G1349D-CFTR. Second, genistein stimulates G551D-CFTR without any inhibition at high concentration The authors conclude from these results that whereas G551 in NBD1 is an important mol. site for inhibition of CFTR by genistein, the sym. G1349 in NBD2 is also one major site but for the activation of CFTR by genistein. Because both mutations alter specifically the mechanism of CFTR channel activation by genistein, the authors believe that the signature sequences of CFTR act as mol. switches that upon interaction with genistein turn on and off the channel.

IT 396712-16-6, MPB-91
RL: BSU (Biological study, unclassified); BIOL (Biological study)

(cystic fibrosis mutation G1349D within signature motif LSHGH of NBD2 abolishes activation of CFTR chloride channels by genistein in relation to)

RN 396712-16-6 CAPLUS

CN Benzo[c]quinolizinium, 5-butyl-10-chloro-6-hydroxy-, chloride (9CI) (CA INDEX NAME)

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REFERENCE COUNT: 31 THERE ARE 31 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 6 OF 20 CAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER: 2004:389460 CAPLUS

DOCUMENT NUMBER: 141:18110

TITLE: Regulation of the cystic fibrosis transmembrane conductance regulator channel by β-adrenergic agonists and vasoactive intestinal peptide in rat smooth muscle cells and its role in vasorelaxation

AUTHOR(S): Robert, Renaud; Thoreau, Vincent; Norez, Caroline; Cantereau, Anne; Kitzis, Alain; Mettey, Yvette; Rogier, Christian; Becq, Frederic

CORPORATE SOURCE: Laboratoire des Biomembranes et Signalisation Cellulaire CNRS Unite Mixte de Recherche 6558, Universite de Poitiers, Poitiers, 86022, Fr.

SOURCE: Journal of Biological Chemistry (2004), 279(20), 21160-21168
CODEN: JBCHA3; ISSN: 0021-9258

PUBLISHER: American Society for Biochemistry and Molecular Biology

DOCUMENT TYPE: Journal

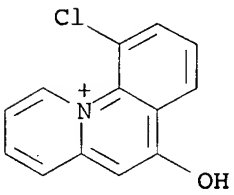
LANGUAGE: English

AB The signaling events that regulate vascular tone include voltage-dependent Ca2+ influx and the activities of various ionic channels, which mol. entities are involved and their role are still a matter of debate. Here the authors show expression of the cystic fibrosis transmembrane conductance regulator (CFTR) Cl- channel in rat aortic smooth muscle cells. Immunopptn. and in vitro protein kinase A phosphorylation show the appearance of mature band C of CFTR. An immunohistochem. study shows CFTR proteins in smooth muscles of aortic rings but not in skeletal muscles. Using the iodide efflux method, a combination of agonists and pharmacol. agents was used to dissect the function of CFTR. Agonists of the cAMP pathway, the β-adrenergic agonist isoproterenol, and the neuropeptide vasoactive intestinal peptide activate CFTR-dependent transport from cells maintained in a high but not low extracellular potassium-rich saline, suggesting that depolarization of smooth muscle is critical to CFTR activation. Smooth muscle CFTR possesses all of the pharmacol. attributes of its epithelial homologs: stimulation by the CFTR pharmacol. activators MPB-07 (EC50 = 158 μM) and MPB-91 (EC50 = 20 μM) and inhibition by

glibenclamide and diphenylamine-2-carboxylic acid but not by 5,11,17,23-tetrasulfonato-25,26,27,28-tetramethoxy-calix[4]arene. Contraction measurements on isolated aortic rings were performed to study the contribution of CFTR to vascular tone. With aortic rings (without endothelium) preconstricted by high K+ saline or by the α-adrenergic agonist norepinephrine, CFTR activators produced a concentration-dependent relaxation. These results identify for the first time the expression and function of CFTR in smooth muscle where it plays an unexpected but fundamental role in the autonomic and hormonal regulation of the vascular tone.

IT 191091-55-1, MPB-07 396712-16-6, MPB-91
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(CFTR pharmacol. activator; β-adrenergic agonists and VIP regulation of CFTR chloride channel in rat smooth muscle cells and its role in vasorelaxation and involved signaling mechanism)

RN 191091-55-1 CAPLUS
CN Benzo[c]quinolizinium, 10-chloro-6-hydroxy-, chloride (1:1) (CA INDEX NAME)

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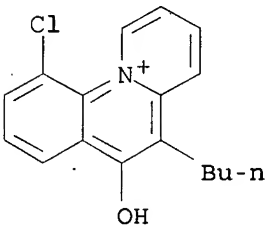
RN 396712-16-6 CAPLUS
CN Benzo[c]quinolizinium, 5-butyl-10-chloro-6-hydroxy-, chloride (9CI) (CA INDEX NAME)

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REFERENCE COUNT: 37 THERE ARE 37 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 7 OF 20 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2004:42547 CAPLUS
DOCUMENT NUMBER: 140:199186
TITLE: Synthesis, SAR, Crystal Structure, and Biological Evaluation of Benzoquinoliziniums as Activators of Wild-Type and Mutant Cystic Fibrosis Transmembrane Conductance Regulator Channels

10/516,839

AUTHOR(S): Marivingt-Mounir, Cecile; Norez, Caroline; Derand, Renaud; Bulteau-Pignoux, Laurence; Nguyen-Huy, Dung; Viossat, Bernard; Morgant, Georges; Becq, Frederic; Vierfond, Jean-Michel; Mettey, Yvette

CORPORATE SOURCE: Laboratoire de Chimie Organique, Faculte de Medecine et de Pharmacie, Universite de Poitiers, Poitiers, 86005, Fr.

SOURCE: Journal of Medicinal Chemistry (2004), 47(4), 962-972
CODEN: JMCMAR; ISSN: 0022-2623

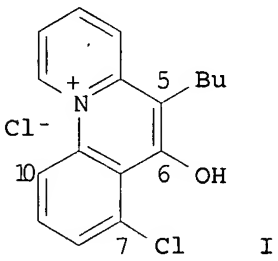
PUBLISHER: American Chemical Society

DOCUMENT TYPE: Journal

LANGUAGE: English

OTHER SOURCE(S): CASREACT 140:199186

GI

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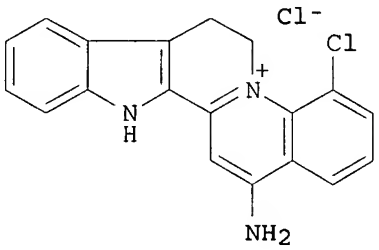


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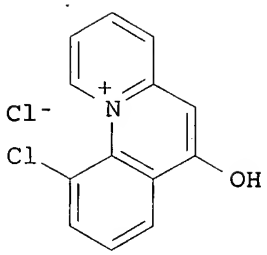


III

AB Chloride channels play important roles in homeostasis and regulate cell volume, transepithelial transport, and elec. excitability. Despite recent progress made in the genetic and mol. aspect of chloride channels, their pharmacol. is still poorly understood. The cystic fibrosis transmembrane conductance regulator (CFTR) is a cAMP-regulated epithelial chloride channel for which mutations cause cystic fibrosis. Here we have synthesized benzo[c]quinolizinium, e.g., I, and benzo[f]indolo[2,3-a]quinolizinium salts (MPB), e.g., II, and performed a SAR to identify the structural basis for activation of the CFTR chloride channel. Synthesized compds. were evaluated on wild-type CFTR and on CFTR having the glycine-to-aspartic acid missense mutation at codon 551 (G551D-CFTR), using a robot and cell-based assay. The presence of an hydroxyl group at position 6 of the benzo[c]quinolizinium skeleton associated with a chlorine atom at position 10 or 7 and an alkyl chain at position 5 determined the highest activity. The most potent product is 5-butyl-7-chloro-6-hydroxybenzo[c]quinolizinium chloride (I, MPB-104). I is 100 times more potent than the parent compound III (MPB-07).

IT 396712-16-6P
RL: ADV (Adverse effect, including toxicity); PAC (Pharmacological activity); PRP (Properties); RCT (Reactant); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent)
(crystal structure; preparation, structure-activity relationship, biol.

L4 ANSWER 8 OF 20 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2003:971589 CAPLUS
DOCUMENT NUMBER: 140:13093
TITLE: Use of benzo[c]quinolizinium derivatives for the treatment of diseases related to smooth muscle cell constriction
INVENTOR(S): Becq, Frederic; Robert, Renaud; Pignoux Bulteau, Laurence; Rogier, Christian; Mettey Renoult, Yvette; Vierfond, Jean Michel; Joffre, Michel; Marivingt, Mounir Cecile
PATENT ASSIGNEE(S): Centre National de la Recherche Scientifique CNRS, Fr.
SOURCE: Fr. Demande, 59 pp.
CODEN: FRXXBL
DOCUMENT TYPE: Patent
LANGUAGE: French
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| FR 2840610 | A1 | 20031212 | FR 2002-6916 | 20020605 |
| WO 2003104228 | A1 | 20031218 | WO 2003-FR1688 | 20030605 |
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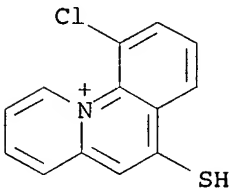
| RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG | | | | |
| AU 2003255646 | A1 | 20031222 | AU 2003-255646 | 20030605 |
| EP 1509520 | A1 | 20050302 | EP 2003-757110 | 20030605 |
| EP 1509520 | B1 | 20061122 | | |
| R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK | | | | |
| AT 346066 | T | 20061215 | AT 2003-757110 | 20030605 |
| US 2005176747 | A1 | 20050811 | US 2005-516839 | 20050304 |
| PRIORITY APPLN. INFO.: | | | FR 2002-6916 A | 20020605 |
| | | | WO 2003-FR1688 W | 20030605 |

OTHER SOURCE(S): MARPAT 140:13093

AB The invention discloses the use of benzo[c]quinolizinium derivs. (preparation included) for the treatment of diseases related to smooth muscle cell constriction, e.g. arterial hypertension and asthma.

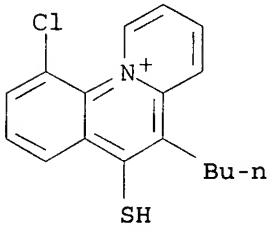
IT 191091-55-1
RL: DMA (Drug mechanism of action); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(benzo[c]quinolizinium derivs. for treatment of diseases related to smooth muscle cell constriction)

RN 191091-55-1 CAPLUS
CN Benzo[c]quinolizinium, 10-chloro-6-hydroxy-, chloride (1:1) (CA INDEX NAME)



● Cl⁻

RN 631842-08-5 CAPLUS
CN Benzo[c]quinolizinium, 5-butyl-10-chloro-6-mercapto-, chloride (9CI) (CA INDEX NAME)



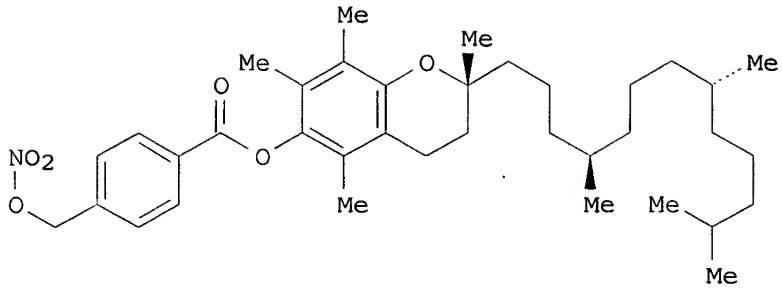
● Cl⁻

REFERENCE COUNT: 1 THERE ARE 1 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 9 OF 20 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2003:652131 CAPLUS
DOCUMENT NUMBER: 139:214237
TITLE: Preparation of nitrate prodrugs able to release nitric oxide in a controlled and selective way and their use for prevention and treatment of inflammatory, ischemic and proliferative diseases
INVENTOR(S): Scaramuzzino, Giovanni
PATENT ASSIGNEE(S): Italy
SOURCE: Eur. Pat. Appl., 313 pp.
CODEN: EPXXDW
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| EP 1336602 | A1 | 20030820 | EP 2002-425075 | 20020213 |
| R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR | | | | |
| PRIORITY APPLN. INFO.: | | | EP 2002-425075 | 20020213 |

GI



II

AB New pharmaceutical compds. of general formula F-(X)q (I) [q = 1-5, preferably 1; F is chosen among drugs such as δ-tocopherol, clidanac, diethylhomospermine, glucosamine, thymocartin, vofopitant, etc.; X is chosen among 4 groups M, T, V, and Y where M = ONO2, nitrate salt, nitrite ester, ONO, thoinitrite, SNO, etc., T = OR1-M, OR1OR1-M, SR1NR2R1-M, NR2R1-M, NR2R1SR1-M, etc., R1 = saturated or unsatd., linear or branched alkylene, having 1 to 21 carbon atoms or a saturated or unsatd., optionally heterosubstituted or branched cycloalkylene, having 3 to 7 carbon atoms or an optionally heterosubstituted arylene having 3 to 7 carbon atoms; R2 = H, saturated or unsatd., linear or branched 1-21 carbon atom alkyl, saturated or unsatd. optionally heterosubstituted or branched 3-7 carbon cycloalkyl, optionally heterosubstituted 3-7 carbon aryl; R1, R2 = OH, SH, F, Cl, Br, OPO3H2, CO2H, etc.; bond between F and T = carboxylic ester, carboxylic amide, glycoside, azo, thioester, sulfonic ester, etc.; V = Z-M2, OZ-M2, NR2Z-M2, R1Z-M2, OR1-M2, OR1Z-M2, M2 = M, R1-M, OR1-M, SR1-M, NR2R1-M; ZM2 = COCH2CH(M2)CH2N+Me3, COCH2CH2COM2, COCH(NHR2)CH2M2, etc.; Y = 4-COC6H4CH2ONO2, O(CH2)4ONO2, COCH(NH2)CH2ONO2, 3-OC6H4CH2ONO2, etc.] were prepared For example, α-tocopherol reacted with 4-HO2CC6H4CH2ONO2 to give the nitroxymethyl derivative II. The compds. of general formula I are nitrate prodrugs which can release nitric oxide in vivo in a controlled and selective way and without hypotensive side effects and for this reason they are useful for the preparation of medicines for prevention and treatment of inflammatory, ischemic, degenerative and proliferative diseases of musculoskeletal, tegumental, respiratory, gastrointestinal, genito-urinary and central nervous systems.

IT 586349-02-2P
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of nitrate prodrugs for treating or preventing inflammatory, ischemic, degenerative, and proliferative diseases)

RN 586349-02-2 CAPLUS

CN Benzo[c]quinolizinium, 10-chloro-6-hydroxy-, nitrate (salt) (9CI) (CA INDEX NAME)

CM 1

CRN 586349-01-1
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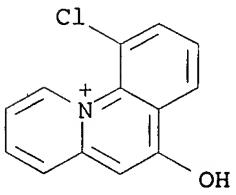
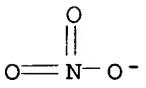


CM 2

CRN 14797-55-8
CMF N O3



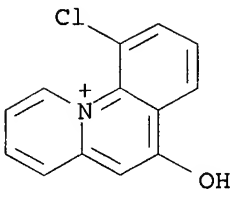
REFERENCE COUNT: 19 THERE ARE 19 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 10 OF 20 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2003:598346 CAPLUS
DOCUMENT NUMBER: 140:70712
TITLE: Inhibition of ATP-sensitive K+ channels by substituted benzo[c]quinolizinium CFTR activators
AUTHOR(S): Prost, Anne-Lise; Derand, Renaud; Gros, Laurent; Becq, Frederic; Vivaudou, Michel
CORPORATE SOURCE: Laboratoire de Biophysique Moleculaire et Cellulaire, CEA, DRDC, Grenoble, 38054, Fr.
SOURCE: Biochemical Pharmacology (2003), 66(3), 425-430
CODEN: BCPCA6; ISSN: 0006-2952
PUBLISHER: Elsevier Science B.V.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The substituted benzo[c]quinolizinium compds. MPB-07 and MPB-91 are novel activators of the cystic fibrosis transmembrane conductance regulator (CFTR) chloride channel. High homologies between CFTR and the sulfonylurea receptor (SUR), which assocs. with the potassium channel Kir6.2 to form the ATP-sensitive K+ (KATP) channel, prompted us to examine possible effects of these compds. on KATP channels using electrophysiol. recordings and binding assays. Activity of recombinant KATP channels expressed in Xenopus oocytes was recorded in the inside-out configuration of the patch-clamp technique. Channels were practically unaffected by MPB-07 but were fully blocked by MPB-91 with half-inhibition achieved at .apprx.20 μM MPB-91. These effects were similar on channels formed by Kir6.2, and either the SUR1 or SUR2A isoforms were independent of the presence of nucleotides. They were not influenced by SUR mutations known to interfere with its nucleotide-binding capacity. MPB-91, but not MPB-07, was able to displace binding of glibenclamide to HEK cells expressing recombinant SUR1/Kir6.2 channels. Glibenclamide binding to native channels from pancreatic MIN6 cells was also displaced by MPB-91. A Kir6.2 mutant able to form channels without SUR was also blocked by MPB-91, but not by MPB-07. These observations demonstrate that neither MPB-07 nor MPB-91 interact with SUR, in spite of its high homol. with CFTR, and that MPB-91 blocks KATP channels by binding to the Kir6.2 subunit. Thus, caution should be exercised when planning to use MPB compds. in cystic fibrosis therapy, specially MPB-91 which could nonetheless find interesting applications as the precursor of a new class of K channel blockers.

IT 191091-55-1, MPB 07 396712-16-6, MPB 91
RL: DMA (Drug mechanism of action); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(inhibition of ATP-sensitive K+ channels by substituted benzo[c]quinolizinium CFTR activators)

RN 191091-55-1 CAPLUS
CN Benzo[c]quinolizinium, 10-chloro-6-hydroxy-, chloride (1:1) (CA INDEX NAME)

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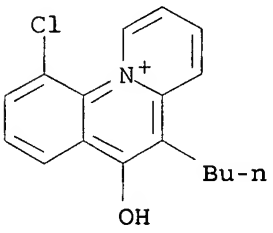
RN 396712-16-6 CAPLUS
CN Benzo[c]quinolizinium, 5-butyl-10-chloro-6-hydroxy-, chloride (9CI) (CA INDEX NAME)

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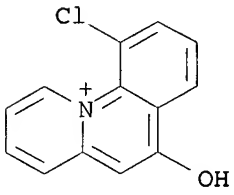
REFERENCE COUNT: 24 THERE ARE 24 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 11 OF 20 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2002:972019 CAPLUS
DOCUMENT NUMBER: 139:63261
TITLE: Benzo(c)quinolizinium drugs inhibit degradation of ΔF508-CFTR cytoplasmic domain
AUTHOR(S): Stratford, Fiona L. L.; Pereira, Malcolm M. C.; Becq, Frederic; McPherson, Margaret A.; Dormer, Robert L.
CORPORATE SOURCE: Department of Medical Biochemistry, University of Wales College of Medicine, Cardiff, CF14 4XN, UK
SOURCE: Biochemical and Biophysical Research Communications (2003), 300(2), 524-530
CODEN: BBRCA9; ISSN: 0006-291X
PUBLISHER: Elsevier Science
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Proteins comprising the first nucleotide-binding- and R-domains of wild-type and ΔF508 cystic fibrosis transmembrane conductance regulator (CFTR) have been synthesized by in vitro transcription/translation. The kinetics and extent of degradation of wild-type and ΔF508 cytoplasmic domain proteins in rabbit reticulocyte lysates, in which proteasome activity was inhibited, were similar, with a half-life of approx. 4 h. The results show for the first time, that the benzo(c)quinolizinium compds., MPB-07 and MPB-91, selectively inhibit degradation of the ΔF508 cytoplasmic domain protein. Studies using protease inhibitors demonstrated that both ΔF508 and

wild-type proteins are substrates for cysteine proteases. The studies provide evidence that benzo(c)quinolizinium compds. protect a proteolytic cleavage site by direct binding to the first cytoplasmic domain of ΔF508-CFTR and this is a likely mechanism for increasing ΔF508-CFTR trafficking in intact cells.

IT 191091-55-1, MPB 07 396712-16-6, MPB 91
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(Benzo(c)quinolizinium drugs inhibit degradation of ΔF508-CFTR cytoplasmic domain)

RN 191091-55-1 CAPLUS
CN Benzo[c]quinolizinium, 10-chloro-6-hydroxy-, chloride (1:1) (CA INDEX NAME)

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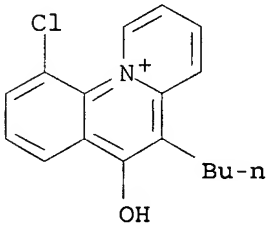
RN 396712-16-6 CAPLUS
CN Benzo[c]quinolizinium, 5-butyl-10-chloro-6-hydroxy-, chloride (9CI) (CA INDEX NAME)

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REFERENCE COUNT: 34 THERE ARE 34 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

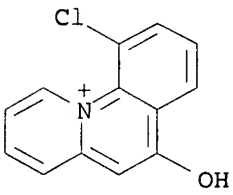
L4 ANSWER 12 OF 20 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2002:140500 CAPLUS
DOCUMENT NUMBER: 137:221898
TITLE: Photodegradation study of a new activator of the cystic fibrosis chloride channel, the 6-hydroxy-10-chlorobenzo[c]quinolizinium chloride (MPB-07)
AUTHOR(S): Olivier, Jean-Christophe; Manceau, Joachim; Marivingt-Mounir, Cecile; Mettey, Yvette; Vierfond, Jean-Michel; Couet, William
CORPORATE SOURCE: Laboratoire de Pharmacie Galenique et Biopharmacie, Faculte de Medecine et Pharmacie, Equipe Medicaments

anti-infectieux et Barriere Hematoencephalique, Poitiers, 86005, Fr.
SOURCE: Journal of Pharmaceutical Sciences (2002), 91(2), 324-330
CODEN: JPMSAE; ISSN: 0022-3549
PUBLISHER: Wiley-Liss, Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The photodegrdn. of 6-hydroxy-10-chlorobenzo[c]quinolizinium chloride (MPB-07), a new activator of the transmembrane conductance regulator chloride channel, was studied in aqueous solns. exposed to artificial daylight (2300 Lx intensity). Various conditions of pH, concentration, and temperature were used. MPB-07 concentration was determined at regular time intervals by reversed-phase HPLC. MPB-07 stability was also studied at pH 7.4 in the dark. Results showed that in all the conditions tested MPB-07 underwent rapid photodegrdn., apparently following first-order kinetics. Rate consts. were dependent on the initial MPB-07 concentration, temperature, and pH. At pH 7.4, and for concns. from 1 to 125 μM, half-lives ranged from 0.681 ± 0.047 to 4.54 ± 0.28 h. The Arrhenius plot was linear and activation energy was calculated to be 20.7 kJ·mol-1. Anal. by chemical ionization-mass spectrometry showed that the chlorine atom of the MPB-07 mol. might be replaced by an OH group during the photodegrdn. process. In the dark, MPB-07 in solns. at pH 7.4 was found to be stable over a 6-wk period. In conclusion, MPB-07 is a highly photolabile mol. that should be carefully protected from light when used.

IT 191091-55-1, MPB 07
RL: PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(photodegrdn. study of activator of cystic fibrosis chloride channel, chlorobenzoquinolizinium chloride)

RN 191091-55-1 CAPLUS
CN Benzo[c]quinolizinium, 10-chloro-6-hydroxy-, chloride (1:1) (CA INDEX NAME)

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REFERENCE COUNT: 12 THERE ARE 12 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

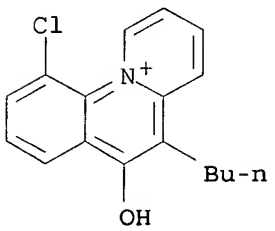
L4 ANSWER 13 OF 20 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2001:906617 CAPLUS
DOCUMENT NUMBER: 136:210359
TITLE: Correction of delF508-CFTR activity with benzo(c)quinolizinium compounds through facilitation of its processing in cystic fibrosis airway cells
AUTHOR(S): Dormer, Robert L.; Derand, Renaud; McNeilly, Ceinwen M.; Mettey, Yvette; Bulteau-Pignoux, Laurence; Metaye, Thierry; Vierfond, Jean-Michel; Gray, Michael A.;

Galietta, Luis J. V.; Morris, M. Rachel; Pereira, Malcolm M. C.; Doull, Iolo J. M.; Becq, Frederic; McPherson, Margaret A.
CORPORATE SOURCE: Department of Medical Biochemistry, University of Wales College of Medicine, Cardiff, CF14 4XN, UK
SOURCE: Journal of Cell Science (2001), 114(22), 4073-4081
CODEN: JNCSAI; ISSN: 0021-9533
PUBLISHER: Company of Biologists Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB A number of genetic diseases, including cystic fibrosis, have been identified as disorders of protein trafficking associated with retention of mutant protein within the endoplasmic reticulum. In the presence of the benzo(c)quinolizinium drugs, MPB-07 and its congener MPB-91, we show the activation of cystic fibrosis transmembrane conductance regulator (CFTR) delF508 channels in IB3-1 human cells, which express endogenous levels of delF508-CFTR. These drugs were without effect on the Ca2+-activated Cl- transport, whereas the swelling-activated Cl- transport was found altered in MPB-treated cells. Immunopptn. and in vitro phosphorylation shows a 20% increase of the band C form of delF508 after MPB treatment. We then investigated the effect of these drugs on the extent of mislocalisation of delF508-CFTR in native airway cells from cystic fibrosis patients. We first showed that delF508 CFTR was characteristically restricted to an endoplasmic reticulum location in approx. 80% of untreated cells from CF patients homozygous for the delF508-CFTR mutation. By contrast, 60-70% of cells from non-CF patients showed wild-type CFTR in an apical location. MPB-07 treatment caused dramatic relocation of delF508-CFTR to the apical region such that the majority of delF508/delF508 CF cells showed a similar CFTR location to that of wild-type. MPB-07 had no apparent effect on the distribution of wild-type CFTR, the apical membrane protein CD59 or the ER membrane Ca2+,Mg-ATPase. We also showed a similar pharmacol. effect in nasal cells freshly isolated from a delF508/G551D CF patient. The results demonstrate selective redirection of a mutant membrane protein using cell-permeant small mols. of the benzo(c)quinolizinium family and provide a major advance towards development of a targetted drug treatment for cystic fibrosis and other disorders of protein trafficking.

IT 396712-16-6, MPB 91
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(MPB 91; correction of delF508-CFTR activity with benzo(c)quinolizinium compds. through facilitation of its processing in cystic fibrosis airway cells)

RN 396712-16-6 CAPLUS
CN Benzo[c]quinolizinium, 5-butyl-10-chloro-6-hydroxy-, chloride (9CI) (CA INDEX NAME)

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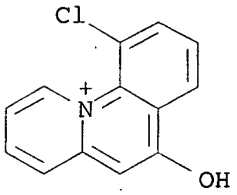
IT 191091-55-1, MPB 07

RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(correction of delF508-CFTR activity with benzo(c)quinolizinium compds. through facilitation of its processing in cystic fibrosis airway cells)

RN 191091-55-1 CAPLUS

CN Benzo[c]quinolizinium, 10-chloro-6-hydroxy-, chloride (1:1) (CA INDEX NAME)

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REFERENCE COUNT: 35 THERE ARE 35 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 14 OF 20 CAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER: 2001:870568 CAPLUS

DOCUMENT NUMBER: 137:276909

TITLE: Localisation of wild-type and ΔF508-CFTR in nasal epithelial cells

AUTHOR(S): Dormer, R. L.; McNeilly, C. M.; Morris, M. R.; Pereira, M. M. C.; Doull, I. J. M.; Becq, F.; Mettey, Y.; Vierfond, J-M.; McPherson, M. A.

CORPORATE SOURCE: Department of Medical Biochemistry, University of Wales College of Medicine, Cardiff, CF14 4XN, UK

SOURCE: Pfluegers Archiv (2001), 443(Suppl. 1), S117-S120
CODEN: PFLABK; ISSN: 0031-6768

PUBLISHER: Springer-Verlag

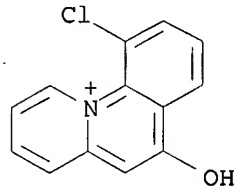
DOCUMENT TYPE: Journal

LANGUAGE: English

AB Wild-type and the ΔF508 mutation of the cystic fibrosis transmembrane conductance regulator (ΔF508-CFTR) were localized by confocal imaging in ΔF508/ΔF508 native airway epithelial cells using a well-characterized CFTR antibody. Surface nasal epithelial cells from three control and three cystic fibrosis individuals were obtained from nasal brushings. Cells were fixed, permeabilized and incubated with first antibody for 18 h at 4°. Following labeling with second antibody, cells were viewed with the confocal microscope. Wild-type CFTR was localized predominantly apically, whereas ΔF508-CFTR was located mainly inside the cell in a region close to the nucleus. Incubation of cells with MPB-07 (250 μM) at 37° for 2 h resulted in pronounced movement of ΔF508-CFTR to the cell periphery, but did not change the localization of wild-type CFTR. The results show that ΔF508-CFTR is mislocalized in native nasal epithelial cells and that its distribution is altered in response to the new CFTR activator, MPB-07. The findings should lead to development of a rational drug treatment for cystic fibrosis patients carrying the ΔF508 mutation.

IT 191091-55-1, MPB 07
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(localization of wild-type and ΔF508-CFTR in nasal epithelial cells and effect of CFTR activator MPB-07 in relation to cystic fibrosis and its treatment)

RN 191091-55-1 CAPLUS
CN Benzo[c]quinolizinium, 10-chloro-6-hydroxy-, chloride (1:1) (CA INDEX NAME)

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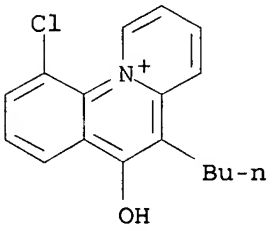
REFERENCE COUNT: 17 THERE ARE 17 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 15 OF 20 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2001:862221 CAPLUS
DOCUMENT NUMBER: 136:161133
TITLE: Activation of G551D CFTR channel with MPB-91: regulation by ATPase activity and phosphorylation
AUTHOR(S): Derand, Renaud; Bulteau-Pignoux, Laurence; Mettey, Yvette; Zegarra-Moran, Olga; Howell, L. Daniel; Randak, Christoph; Galietta, Luis J. V.; Cohn, Jonathan A.; Norez, Caroline; Romio, Leila; Vierfond, Jean-Michel; Joffre, Michel; Becq, Frederic
CORPORATE SOURCE: Laboratoire de Physiologie des Regulations Cellulaires, Unite Mixte de Recherche 6558, Poitiers, 86022, Fr.
SOURCE: American Journal of Physiology (2001), 281(5, Pt. 1), C1657-C1666
CODEN: AJPHAP; ISSN: 0002-9513
PUBLISHER: American Physiological Society
DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 136:161133

AB We have designed and synthesized benzo[c]quinolizinium derivs. and evaluated their effects on the activity of G551D cystic fibrosis transmembrane conductance regulator (CFTR) expressed in Chinese hamster ovary and Fisher rat thyroid cells. We demonstrated, using iodide efflux, whole cell patch clamp, and short-circuit recordings, that 5-butyl-6-hydroxy-10-chlorobenzo[c]quinolizinium chloride (MPB-91) restored the activity of G551D CFTR (EC50 = 85 μM) and activated CFTR in Calu-3 cells (EC50 = 47 μM). MPB-91 has no effect on the ATPase activity of wild-type and G551D NBD1/R/GST fusion proteins or on the ATPase, GTPase, and adenylate kinase activities of purified NBD2. The activation of CFTR by MPB-91 is independent of phosphorylation because (1) kinase inhibitors have no effect and (2) the compound still activated CFTR having 10 mutated protein kinase A sites (10SA-CFTR). The new pharmacol. agent MPB-91 may be an important candidate drug to ameliorate the ion transport defect associated with CF and to point out a new pathway to modulate CFTR activity.

IT 396712-16-6P, MPB 91
RL: DMA (Drug mechanism of action); PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of MPB-91 and activation of G551D CFTR channel)
RN 396712-16-6 CAPLUS

CN Benzo[c]quinolizinium, 5-butyl-10-chloro-6-hydroxy-, chloride (9CI) (CA INDEX NAME)

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REFERENCE COUNT: 33 THERE ARE 33 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

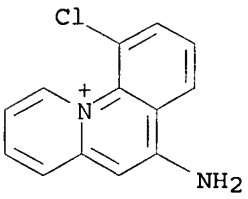
L4 ANSWER 16 OF 20 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1999:637696 CAPLUS
DOCUMENT NUMBER: 131:331747
TITLE: Development of substituted benzo[c]quinolizinium compounds as novel activators of the cystic fibrosis chloride channel
AUTHOR(S): Becq, Frederic; Mettey, Yvette; Gray, Mike A.; Galietta, Luis J. V.; Dormer, Robert L.; Merten, Marc; Metaye, Thierry; Chappe, Valerie; Marvingt-Mounir, Cecie; Zegarra-Moran, Olga; Tarran, Robert; Bulteau, Laurence; Derand, Renaud; Pereira, Malcome M. C.; McPherson, Margaret A.; Rogier, Christian; Joffre, Michel; Argent, Barry E.; Sarrouilhe, Denis; Kammouni, Wafa; Figarella, Catherine; Verrier, Bernard; Gola, Maurice; Vierfond, Jean-Michel
CORPORATE SOURCE: Laboratoire de neurobiologie UPR-9024 CNRS, Marseille, F-13402, Fr.
SOURCE: Journal of Biological Chemistry (1999), 274(39), 27415-27425
CODEN: JBCHA3; ISSN: 0021-9258
PUBLISHER: American Society for Biochemistry and Molecular Biology
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Chloride channels play an important role in the physiol. and pathophysiol. of epithelia, but their pharmacol. is still poorly developed. We have chemical synthesized a series of substituted benzo[c]quinolizinium (MPB) compds. Among them, 6-hydroxy-7-chlorobenzo[c]quinolizinium (MPB-27) and 6-hydroxy-10-chlorobenzo[c]quinolizinium (MPB-07), which we show to be potent and selective activators of the cystic fibrosis transmembrane conductance regulator (CFTR) chloride channel. We examined the effect of MPB compds. on the activity of CFTR channels in a variety of established epithelial and nonepithelial cell systems. Using the iodide efflux technique, we show that MPB compds. activate CFTR chloride channels in Chinese hamster ovary (CHO) cells stably expressing CFTR but not in CHO cells lacking CFTR. Single and whole cell patch clamp recordings from CHO cells confirm that CFTR is the only channel activated by the drugs. Ussing chamber expts. reveal that the apical addition of MPB to human nasal epithelial cells produces a large increase of the short circuit current. This current can be totally inhibited by glibenclamide. Whole cell expts. performed on native respiratory cells isolated from wild type and CF null

mice also show that MPB compds. specifically activate CFTR channels. The activation of CFTR by MPB compds. was glibenclamide-sensitive and 4,4'-diisothiocyanostilbene-2,2'-disulfonic acid-insensitive. In the human tracheal gland cell line MM39, MPB drugs activate CFTR channels and stimulate the secretion of the antibacterial secretory leukoproteinase inhibitor. In submandibular acinar cells, MPB compds. slightly stimulate CFTR-mediated submandibular mucin secretion without changing intracellular cAMP and ATP levels. Similarly, in CHO cells MPB compds. have no effect on the intracellular levels of cAMP and ATP or on the activity of various protein phosphatases (PP1, PP2A, PP2C, or alkaline phosphatase). Our results provide evidence that substituted benzo[c]quinolizinium compds. are a novel family of activators of CFTR and of CFTR-mediated protein secretion and therefore represent a new tool to study CFTR-mediated chloride and secretory functions in epithelial tissues.

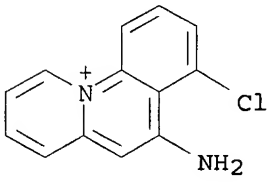
IT 191091-46-0P 191091-50-6P 191091-55-1P
191091-58-4P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(substituted benzo[c]quinolizinium compds. as activators of cystic fibrosis chloride channel)

RN 191091-46-0 CAPLUS
CN Benzo[c]quinolizinium, 6-amino-10-chloro-, chloride (9CI) (CA INDEX NAME)




● $Cl^-$

RN 191091-50-6 CAPLUS
CN Benzo[c]quinolizinium, 6-amino-7-chloro-, chloride (1:1) (CA INDEX NAME)




● $Cl^-$

RN 191091-55-1 CAPLUS
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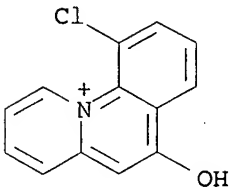
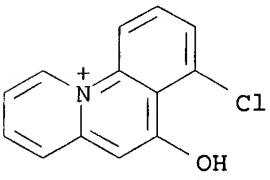


● Cl⁻

RN 191091-58-4 CAPLUS
CN Benzo[c]quinolizinium, 7-chloro-6-hydroxy-, chloride (9CI) (CA INDEX NAME)



● Cl⁻

REFERENCE COUNT: 49 THERE ARE 49 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

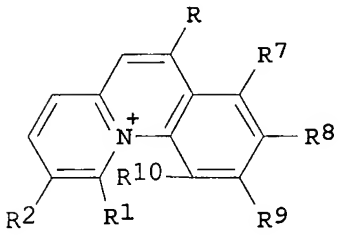
L4 ANSWER 17 OF 20 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1998:112345 CAPLUS
DOCUMENT NUMBER: 128:167362
TITLE: Preparation of benzo[c]quinolizinium salts and analogs as CFTR channel activators
INVENTOR(S): Becq, Frederic; Mettey, Yvette; Vierfond, Jean-Michel; Verrier, Bernard; Gola, Maurice
PATENT ASSIGNEE(S): Centre National de la Recherche Scientifique, Fr.; Becq, Frederic; Mettey, Yvette; Vierfond, Jean-Michel; Verrier, Bernard; Gola, Maurice
SOURCE: PCT Int. Appl., 128 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: French
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| WO 9805642 | A1 | 19980212 | WO 1997-FR1436 | 19970731 |
| W: CA, JP, US | | | | |
| RW: AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE | | | | |
| FR 2751969 | A1 | 19980206 | FR 1996-9721 | 19960801 |
| FR 2751969 | B1 | 19981204 | | |
| CA 2258924 | A1 | 19980212 | CA 1997-2258924 | 19970731 |
| EP 937044 | A1 | 19990825 | EP 1997-936724 | 19970731 |
| EP 937044 | B1 | 20020130 | | |
| R: CH, DE, FR, GB, IT, LI | | | | |

| | | | | | |
|---|---|---|---|---|---|
| JP 2000515863 | T | 20001128 | JP 1998-507677 | | 19970731 |
| US 6630482 | B1 | 20031007 | US 1999-230747 | | 19990302 |
| PRIORITY APPLN. INFO.: | | | FR 1996-9721 | A | 19960801 |
| | | | WO 1997-FR1436 | W | 19970731 |

OTHER SOURCE(S): MARPAT 128:167362


GI



I


AB Title compds. (e.g., I.X; R1,R2 = H; R1R2 = atoms to complete a 6-membered aromatic ring; R7-R10 = H; 1 of R7-R10 may = halo; X = halide ion, CLO4-, etc.) were prepared Thus, 2-ClC6H4CN was cyclocondensed with 2-methylpyridine to give I.Cl-. Data for biol. activity of title compds. were given.


IT 71711-63-2P 71711-65-4P 71711-67-6P
191091-45-9P 191091-46-0P 191091-48-2P
191091-50-6P 191091-53-9P 191091-55-1P
191091-56-2P 191091-58-4P 191091-60-8P
203051-98-3P 203052-17-9P 203052-18-0P
203052-19-1P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of benzo[c]quinolizinium salts and analogs as CFTR channel activators)

RN 71711-63-2 CAPLUS
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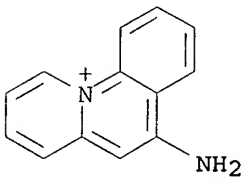

● Cl⁻

RN 71711-65-4 CAPLUS
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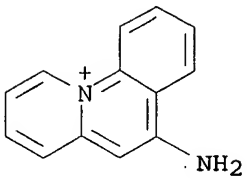
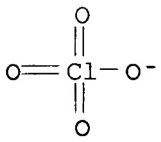
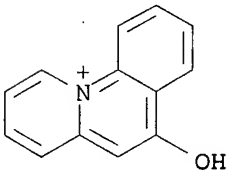


CM 2

CRN 14797-73-0
CMF Cl O4

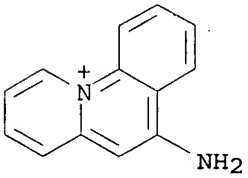


RN 71711-67-6 CAPLUS
CN Benzo[c]quinolizinium, 6-hydroxy-, chloride (9CI) (CA INDEX NAME)



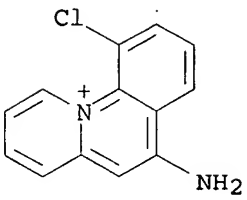
● Cl⁻

RN 191091-45-9 CAPLUS
CN Benzo[c]quinolizinium, 6-amino-, bromide (9CI) (CA INDEX NAME)



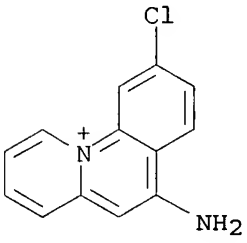
● Br⁻

RN 191091-46-0 CAPLUS
CN Benzo[c]quinolizinium, 6-amino-10-chloro-, chloride (9CI) (CA INDEX NAME)



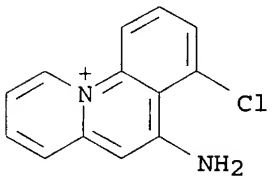
● Cl⁻

RN 191091-48-2 CAPLUS
CN Benzo[c]quinolizinium, 6-amino-9-chloro-, chloride (9CI) (CA INDEX NAME)



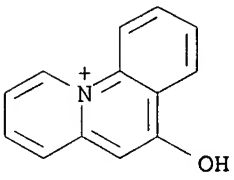
● Cl⁻

RN 191091-50-6 CAPLUS
CN Benzo[c]quinolizinium, 6-amino-7-chloro-, chloride (1:1) (CA INDEX NAME)



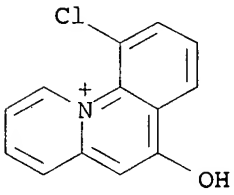
● Cl⁻

RN 191091-53-9 CAPLUS
CN Benzo[c]quinolizinium, 6-hydroxy-, bromide (9CI) (CA INDEX NAME)



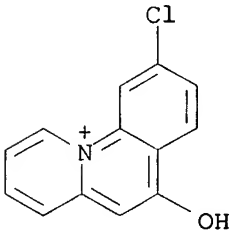
● $Br^-$

RN 191091-55-1 CAPLUS
CN Benzo[c]quinolizinium, 10-chloro-6-hydroxy-, chloride (1:1) (CA INDEX NAME)



● $Cl^-$

RN 191091-56-2 CAPLUS
CN Benzo[c]quinolizinium, 9-chloro-6-hydroxy-, chloride (9CI) (CA INDEX NAME)



● $Cl^-$

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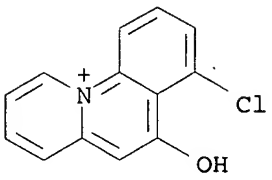
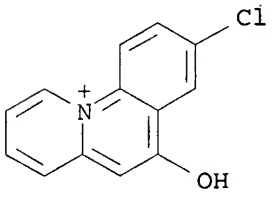
CN Benzo[c]quinolizinium, 7-chloro-6-hydroxy-, chloride (9CI) (CA INDEX NAME)




● $Cl^-$

RN 191091-60-8 CAPLUS
CN Benzo[c]quinolizinium, 8-chloro-6-hydroxy-, chloride (9CI) (CA INDEX NAME)




● $Cl^-$

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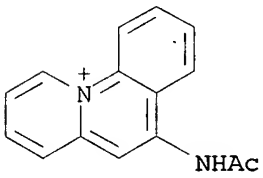


● $Cl^-$

RN 203052-17-9 CAPLUS
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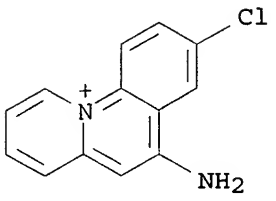

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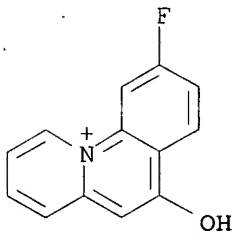

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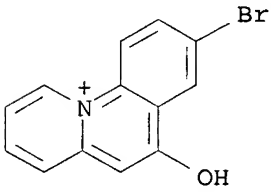


● Cl⁻

REFERENCE COUNT: 12 THERE ARE 12 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

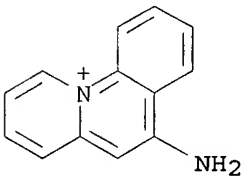
L4 ANSWER 18 OF 20 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1997:330878 CAPLUS
DOCUMENT NUMBER: 127:50527
TITLE: Benzo[c]quinoliziniums: a new family of inhibitors for protein kinase CKII
AUTHOR(S): Mettey, Y.; Vierfond, J-M.; Baudry, M.; Cochet, C.; Sarrouilhe, D.
CORPORATE SOURCE: Laboratoire de Chimie Organique, Faculte de Medecine et de Pharmacie, POITIERS, 86005, Fr.

SOURCE: Bioorganic & Medicinal Chemistry Letters (1997), 7(8), 961-964
CODEN: BMCLE8; ISSN: 0960-894X
PUBLISHER: Elsevier
DOCUMENT TYPE: Journal
LANGUAGE: English

AB A series of bicyclic enols and tricyclic benzo[c]quinoliziniums were prepared and evaluated as inhibitors of protein kinase CKII. Of the seventeen derivs. examined, 6-hydroxybenzo[c]quinolizinium was the most potent inhibitor and exhibited a good selectivity for CKII in the micromolar range.

IT 71711-63-2P 71711-67-6P 191091-45-9P
191091-46-0P 191091-48-2P 191091-50-6P
191091-53-9P 191091-55-1P 191091-56-2P
191091-58-4P 191091-60-8P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(preparation of benzo[c]quinoliziniums as inhibitors for protein kinase CKII)

RN 71711-63-2 CAPLUS
CN Benzo[c]quinolizinium, 6-amino-, chloride (9CI) (CA INDEX NAME)



● Cl⁻

RN 71711-67-6 CAPLUS
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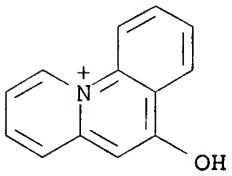
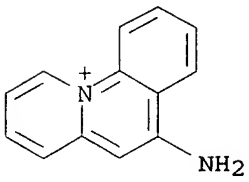


● Cl⁻

RN 191091-45-9 CAPLUS
CN Benzo[c]quinolizinium, 6-amino-, bromide (9CI) (CA INDEX NAME)



● $Br^-$

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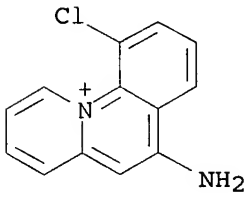

● $Cl^-$

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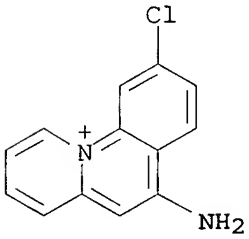
CN Benzo[c]quinolizinium, 6-amino-9-chloro-, chloride (9CI) (CA INDEX NAME)



● $Cl^-$

RN 191091-50-6 CAPLUS
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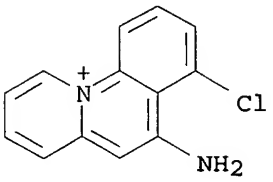

● $Cl^-$

RN 191091-53-9 CAPLUS
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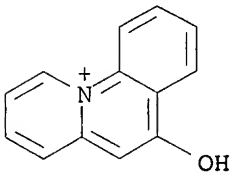

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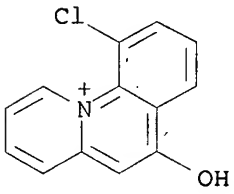

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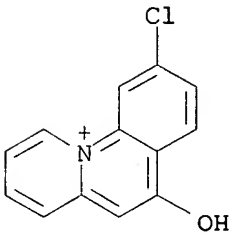


● Cl⁻

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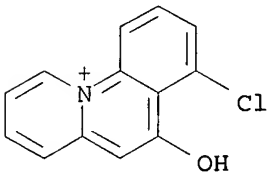


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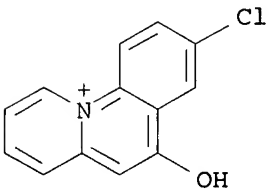


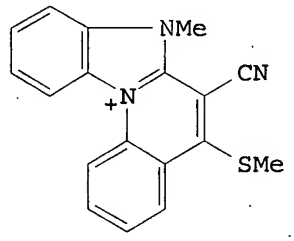

● Cl⁻

REFERENCE COUNT: 11 THERE ARE 11 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 19 OF 20 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1990:216778 CAPLUS
DOCUMENT NUMBER: 112:216778
TITLE: The reaction of S-alkyl salts of condensed azahetarenopyridines containing an angular nitrogen atom
AUTHOR(S): Babichev, F. S.; Volovenko, Yu. M.; Nemazanyi, A. G.; Nemaa, Bushra

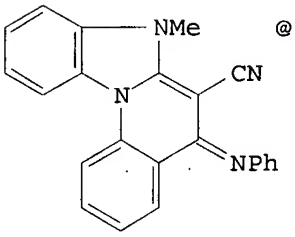
10/516,839

CORPORATE SOURCE: Kiev. Gos. Univ., Kiev, USSR
SOURCE: Ukrainskii Khimicheskii Zhurnal (Russian Edition) (1989), 55(8), 839-41
CODEN: UKZHAU; ISSN: 0041-6045
DOCUMENT TYPE: Journal
LANGUAGE: Russian
OTHER SOURCE(S): CASREACT 112:216778
GI




$4\text{-}MeC_6H_4SO_3^-$

I




@ $4\text{-}MeC_6H_4SO_3H$

II

AB Several reactions of the title salts, e.g., I, were examined Thus, I reacted with PhNH2 to give 86% II.

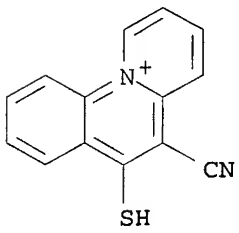
IT 126954-29-8DP, S-alkyl derivs.
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation and reaction of)

RN 126954-29-8 CAPLUS

CN Benzo[c]quinolizinium, 5-cyano-6-mercapto-, salt with 4-methylbenzenesulfonic acid (1:1) (9CI) (CA INDEX NAME)

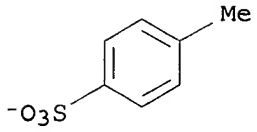
CM 1

CRN 126954-28-7
CMF C14 H9 N2 S

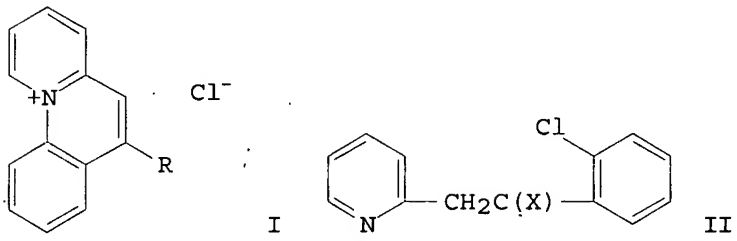



CM 2

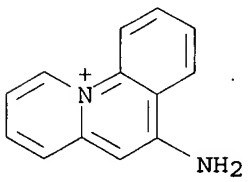
CRN 16722-51-3
CMF C7 H7 O3 S



L4 ANSWER 20 OF 20 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1979:575163 CAPLUS
DOCUMENT NUMBER: 91:175163
ORIGINAL REFERENCE NO.: 91:28251a,28254a
TITLE: Synthesis of derivatives of benzo[c]quinolizine
AUTHOR(S): Vierfond, Jean Michel; Mettey, Yvette; Joubin, Raymond; Miocque, Marcel
CORPORATE SOURCE: Fac. Med. Pharm., Poitiers, 86000, Fr.
SOURCE: Journal of Heterocyclic Chemistry (1979), 16(4), 753-5
CODEN: JHTCAD; ISSN: 0022-152X
DOCUMENT TYPE: Journal
LANGUAGE: French
OTHER SOURCE(S): CASREACT 91:175163
GI



AB The benzoquinolizinium chlorides I (R = NH2OH) were prepared by treating 2-picoline with 2-ClC6H4CN in the presence of PhLi and cyclizing II (X = NH, O) resp. II (X = NH) is easily hydrolyzed to II (X = O). γ-Aminodibenzo[c,f]quinolizinium chloride was similarly prepared from quinaldine.
IT 71711-63-2P 71711-65-4P 71711-67-6P
71711-69-8P 71711-70-1P 71711-73-4P
RL: SPN (Synthetic preparation); PREP (Preparation)
(preparation of)
RN 71711-63-2 CAPLUS
CN Benzo[c]quinolizinium, 6-amino-, chloride (9CI) (CA INDEX NAME)

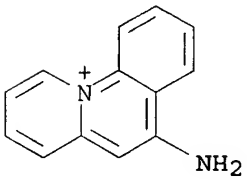


● Cl⁻

RN 71711-65-4 CAPLUS
CN Benzo[c]quinolizinium, 6-amino-, perchlorate (9CI) (CA INDEX NAME)

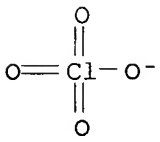
CM 1

CRN 71711-64-3
CMF C13 H11 N2

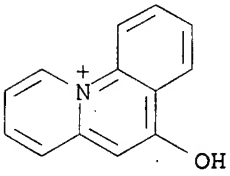


CM 2

CRN 14797-73-0
CMF Cl O4



RN 71711-67-6 CAPLUS
CN Benzo[c]quinolizinium, 6-hydroxy-, chloride (9CI) (CA INDEX NAME)

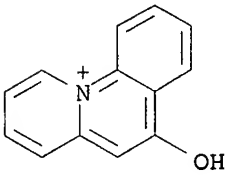


● Cl⁻

RN 71711-69-8 CAPLUS
CN Benzo[c]quinolizinium, 6-hydroxy-, perchlorate (salt) (9CI) (CA INDEX NAME)

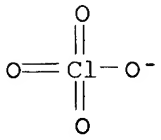
CM 1

CRN 71711-68-7
CMF C13 H10 N O



CM 2

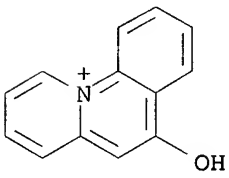
CRN 14797-73-0
CMF Cl O4



RN 71711-70-1 CAPLUS
CN Benzo[c]quinolizinium, 6-hydroxy-, sulfate (1:1) (salt) (9CI) (CA INDEX NAME)

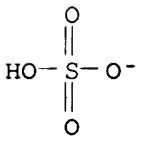
CM 1

CRN 71711-68-7
CMF C13 H10 N O



CM 2

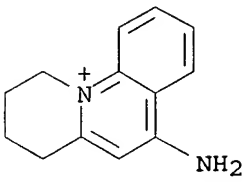
CRN 14996-02-2
CMF H O4 S



RN 71711-73-4 CAPLUS
CN Benzo[c]quinolizinium, 6-amino-1,2,3,4-tetrahydro-, perchlorate (9CI) (CA INDEX NAME)

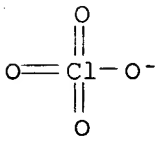
CM 1

CRN 71711-72-3
CMF C13 H15 N2



CM 2

CRN 14797-73-0
CMF Cl O4



=> d his

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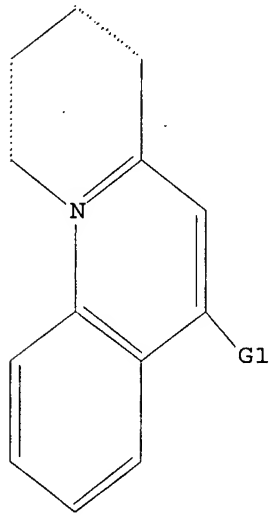
FILE 'REGISTRY' ENTERED AT 10:44:23 ON 26 DEC 2007
L1 STRUCTURE UPLOADED
L2 3 S L1
L3 75 S L1 FULL

FILE 'CAPLUS' ENTERED AT 10:44:52 ON 26 DEC 2007
L4 20 S L3

=> d l1
L1 HAS NO ANSWERS
L1 STR



G1 O,S,N

Structure attributes must be viewed using STN Express query preparation.

=>